SCIENTIFIC LETTER

Persistent endothelial dysfunction in calcified aortic stenosis beyond valve replacement surgery

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The leading cause of aortic valve morbidity in industrialised nations is degenerative calcified aortic stenosis. A convincing body of evidence suggests the concept that degenerative aortic stenosis represents a form of atherosclerotic vascular disease.[1] Endothelial dysfunction promoting abnormal vasomotion, increased leucocyte adhesion, platelet dysfunction and vascular inflammation, which have been shown extensively in atherosclerosis, was recently found in degenerative aortic valve disease.[2] Decreased nitric oxide (NO) bioavailability has a pivotal role in this process, and is largely determined by the expression of endothelial nitric oxide synthase (eNOS). Interestingly, eNOS expression is markedly influenced by haemodynamic factors, as shear stress is the main physiological trigger to enhance eNOS expression and activity.[3] In the study by Poggianti *et* al,[2] the effects of haemodynamic parameters have not been discussed as only patients with aortic valve sclerosis but without relevant haemodynamic stenosis were studied. We hypothesised that altered haemodynamics in aortic stenosis may at least partly be responsible for endothelial dysfunction and thus potentially normalise after aortic-valve replacement. Increased low-grade systemic inflammation has also been shown in aortic stenosis[4] and consequently would be expected to influence vascular function similar to that described in coronary artery disease. Thus, we investigated endothelial dysfunction and signs of inflammation in haemodynamically relevant degenerative aortic stenosis before and after valve replacement.

METHODS

Patients with mean transvalvular pressure gradient >35 mm Hg awaiting open heart valve surgery were included. Exclusion criteria were more than one stenosis >25% on coronary angiography, ankle brachial index <0.8, rheumatic or bicuspid aortic valve disease, concomitant infection, chronic inflammatory diseases, surgery in the past 6 months and neoplastic disorders. Individual medical treatment was not withheld for the study protocol. Fifteen healthy subjects matched for age and cardiovascular risk factors (fasting plasma glucose >7.0 mmol/l, blood pressure >140/90 mm Hg, plasma low-density lipoprotein-cholesterol >4.0 mmol/l, >5 cigarettes/day, coronary artery disease in a family member) served as controls. Written informed consent was obtained from all participants prior to participation in the study. The study was approved by the local ethics committee.

Endothelial function was assessed with a 10 MHz linear array transducer. Flow-mediated dilatation (FMD) of the brachial artery was induced by release of a forearm cuff inflated to suprasystolic pressure for 5 min. Glyceryl trinitrate (0.4 mg) given sublingually served as an endothelium-independent vasodilator. Centreline blood-flow velocity was measured continuously at baseline and after forearm cuff deflation assessing peak flow. Systolic vessel wall distension and raise time (duration of the anacrotic limb of the pulse wave) were computed offline. Study visits were scheduled before and on average 5.3 months after valve-replacement surgery.

Results were presented as means (standard deviation (SD)) except for levels of C reactive protein (CRP), where medians and interquartile range (between 25th and 75th centiles) were used. FMD and glyceryl trinitrate-induced vasodilatation were calculated as the percentage change from baseline diameter. Two-sided paired and unpaired Student's t tests, Wilcoxon signed rank test or Mann–Whitney test were used for intragroups and intergroup comparisons. A p value <0.05 was considered significant.

RESULTS

In all, 15 patients (62 (10) years) and 15 controls (60 (10) years; $p = 0.63$) adhered to the complete study protocol. Mean (SD) valve area before surgery was 0.6 (0.2) cm^2 and mean (SD) transvalvular pressure gradient was 61 (21) mm Hg; 3 patients took both low-dose aspirin and statin, 9 received angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers and 11 received β-blockers. Statin treatment was newly given in one patient and aspirin was discontinued in two patients at follow-up. Cardiovascular risk factors were comparable between patients and controls (1.4 (1.1) *v* 1.0 (1.0); $p = 0.39$). Table 1 shows the results of haemodynamic variables, blood chemistry and vascular function.

FMD expressed in absolute values showed similar results (patients before surgery 90 μm, controls 132 μm, $p = 0.02$; patients after surgery 92 μm, intragroup $p = 0.85$). Change in vessel-wall diameter was not related to the change in FMD ($r = 0.24$, $p = 0.37$). CRP levels were inversely correlated with FMD ($r = 0.4$, $p = 0.03$).

DISCUSSION

We found endothelial dysfunction in degenerative aortic stenosis in association with increased plasma levels of CRP compared with matched controls. Despite normalisation of haemodynamic parameters after valve replacement, endothelial function showed no improvement. Our results suggest an ongoing disease process that may not be entirely halted by removal of the diseased valve, similar to that described in atherosclerosis, where restoration of normal vessel lumen resolves the symptoms but does not necessarily change the course of the disease.

The typical pulsus ''parvus et tardus'' in aortic stenosis could not be shown to the extent documented in the literature. However, reduced shear stress is suggested by the finding of greater vessel diameter in aortic stenosis at baseline and similar blood flow profiles compared with controls. Despite normalisation of vessel diameter and wall distension after correction of stenosis, endothelial function remained depressed. In line with this finding, Poggianti *et al*[2]

Abbreviations: CRP, C reactive protein; eNOS, endothelial nitric oxide synthase; FMD, flow-mediated dilatation

Table 1 Results of haemodynamic variables, blood chemistry and vascular function

		Degenerative aortic stenosis			
	Controls n = 15	Before surgery n = 15	After surgery n = 15	p_1 Intergroup	p_2 Intragroup
Haemodynamic variables					
Systolic blood pressure (mm Hg)	128 (18)	130 (18)	133 (19)	0.83	0.98
Diastolic blood pressure (mm Hg)	80 (9)	82 (10)	80 (13)	0.61	0.38
Heart rate (bpm)	61 (11)	69 (9)	69 (9)	0.08	0.84
Left-ventricular septum thickness (cm)	—	1.57 (0.24)	1.40 (0.19)	—	0.01*
Ejection fraction (%)	—	60 (11)	65 (12)	—	0.09
Brachial artery blood flow at rest (m/s)	0.13 (0.04)	0.15 (0.05)	0.14 (0.06)	0.51	0.77
Brachial artery peak blood (m/s)	0.69 (0.11)	0.68 (0.20)	0.66 (0.20)	0.93	0.87
Laboratory parameters					
Cholesterol (mmol/l)	5.7 (1.1)	5.3 (0.9)	4.9 (0.7)	0.40	0.43
High-density lipoprotein-cholesterol (mmol/l)	1.6 (0.5)	1.5 (0.4)	1.4 (0.3)	0.83	0.28
Low-density lipoprotein-cholesterol (mmol/l)	3.3 (1.1)	3.1 (0.9)	2.7 (0.6)	0.77	0.33
Triglycerides (mmol/l)	1.8 (1.2)	1.3 (0.5)	1.8 (1.0)	0.21	0.14
Creatinine (μmol/l)	88 (13)	90 (19)	90 (12)	0.69	0.96
Glucose (mmol/l)	5.0 (0.5)	5.3 (0.6)	5.1 (0.7)	0.20	0.31
C reactive protein (mg/l)	0.9 (0.4–1.6)	4.0 (1.0–5.2)	3.1 (1.4–4.2)	0.003*	0.55
Vascular function					
Baseline diameter (mm)	3.48 (0.68)	4.17 (0.65)	3.71 (0.66)	0.01*	0.03*
Flow-mediated vasodilatation (%)	4.0 (1.5)	2.2 (1.3)	2.5 (1.3)	0.001*	0.37
Glyceryl trinitrate-induced vasodilatation (%)	14.0 (4.2)	9.4 (5.6)	11.9 (3.1)	0.08	0.37
Systolic vessel wall distension (μm)	180 (18)	139 (12)	190 (24)	0.08	0.03*
Raise time (ms)	221 (13)	248 (21)	207 (16)	0.35	0.15

Data are mean (SD) or median (range).
*$p<0.05$.
p_1, comparison between controls and degenerative aortic stenosis before surgery; p_2, comparison of degenerative aortic stenosis before and after surgery.

found endothelial dysfunction in haemodynamically non-relevant aortic valve sclerosis. Therefore, factors other than haemodynamic parameters may be accountable for endothelial dysfunction in degenerative aortic stenosis, possibly increased levels of CRP, which were inversely correlated with FMD in our study as shown previously in atherosclerosis.[5] Recent data show the ability of CRP to directly down regulate the expression of eNOS, leading to diminished NO bioavailability. CRP levels were higher than in controls matched for age and cardiovascular risk factors, suggesting a pronounced activation of inflammation, unexplained by hypertension, hypercholesterolaemia and diabetes. Aortic stenosis is associated with aortic plaques in 90% of the patients and removal of the diseased valve may not completely eliminate the inflamed tissue mediating synthesis of CRP.

With the down regulation of eNOS, as suggested by our data, and increased sympathetic activity due to heart failure, reduced vessel diameters in aortic stenosis would be expected. The finding of increased luminal diameter is therefore surprising and may be mediated by the local accumulation of metabolic waste products (ADP, CO_2 and H^+) and NO release due to turbulent post-stenotic blood flow. Outward remodelling as observed in atherosclerosis seems unlikely, as normalisation within 5 months would not be expected.

There are limitations to our study: endothelial function measurements may have been influenced by heart failure, often present in latestage aortic stenosis, and underlying relevant atherosclerotic vascular disease that is not detectable by coronary angiography.

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